# Perivascular stem cells: a prospectively purified mesenchymal stem cell population for bone tissue engineering.

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**Public Summary:**
An ideal mesenchymal stem cell (MSC) source for bone tissue engineering has yet to be identified. Such an MSC population would be easily harvested in abundance, with minimal morbidity and with high purity. Our laboratories have identified perivascular stem cells (PSCs) as a candidate cell source. PSCs are readily isolatable (through fluorescent activated cell sorting) from adipose tissue and have been previously shown to be indistinguishable in phenotype and differentiation potential to MSCs. In the present study we directly compare the bone-forming capability of PSCs to an unsorted population, termed stromal vascular fraction (or SVF). We found that the purified PSCs out-performed the unpurified SVF population in terms of bone formation. This was determined through the use of an intramuscular implantation model. Finally, a novel osteoinductive protein (NELL-1) was shown to synergistic enhance PSC-mediated bone formation. These results suggest that both PSCs alone, or PSCs with NELL-1, have promise for future efforts in stem cell mediated bone repair.

**Scientific Abstract:**
Adipose tissue is an ideal source of mesenchymal stem cells for bone tissue engineering: it is largely dispensable and readily accessible with minimal morbidity. However, the stromal vascular fraction (SVF) of adipose tissue is a heterogeneous cell population, which leads to unreliable bone formation. In the present study, we prospectively purified human perivascular stem cells (PSCs) from adipose tissue and compared their bone-forming capacity with that of traditionally derived SVF. PSCs are a population (sorted by fluorescence-activated cell sorting) of pericytes (CD146+CD34-CD45-) and adventitial cells (CD146-CD34+CD45-), each of which we have previously reported to have properties of mesenchymal stem cells. Here, we found that PSCs underwent osteogenic differentiation in vitro and formed bone after intramuscular implantation without the need for predifferentiation. We next sought to optimize PSCs for in vivo bone formation, adopting a demineralized bone matrix for osteoinduction and tricalcium phosphate particle formulation for protein release. Patient-matched, purified PSCs formed significantly more bone in comparison with traditionally derived SVF by all parameters. Recombinant bone morphogenetic protein 2 increased in vivo bone formation but with a massive adipogenic response. In contrast, recombinant Nel-like molecule 1 (NELL-1; a novel osteoinductive growth factor) selectively enhanced bone formation. These studies suggest that adipose-derived human PSCs are a new cell source for future efforts in skeletal regenerative medicine. Moreover, PSCs are a stem cell-based therapeutic that is readily approvable by the U.S. Food and Drug Administration, with potentially increased safety, purity, identity, potency, and efficacy. Finally, NELL-1 is a candidate growth factor able to induce human PSC osteogenesis.